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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/531,660	04/15/2005	Luis Molina	11299.105005	3876
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KING & SPALDING 1180 PEACHTREE STREET, NE ATLANTA, GA 30309-3521			EXAMINER CORDERO GARCIA, MARCELA M	
			ART UNIT 1654	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/531,660

Applicant(s)

MOLINA, LUIS

ExaminerMARCELA M. CORDERO
GARCIA**Art Unit**

1654

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-11 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-11 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date ____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date ____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: ____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2 March 2009 has been entered.

Status of the claims

Claims 1-11 are pending in the application. Claims 1-11 are presented for examination on the merits as they read upon the species: a method of treating dry eye disease comprising administering to a subject in need of such treatment a therapeutically effective amount of duramycin in a saline solution via topical administration. Additionally, for the sake of compact prosecution, other species (lysostaphin, nisin, cinnamycin, ancovenin and Pep 5) have been found during the search, which are also examined herein.

Any rejection from the previous office action, which is not restated here, is withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient."

MPEP 2163. Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to a method of treating dry eye disease comprising administering to a subject in need of such treatment a

therapeutically effective amount of a lantibiotic in a pharmaceutically effective carrier. With regards to the term "lantibiotic", the disclosure teaches that "Lantibiotics that may be used to carry out the present invention include, but are not limited to, duramycin, nisin, subtilin (Gross et al. Z. Physiol. Chem., 354, 810 (1973)), epidermin (Schnell et al. Nature, 333,276 (1988)), Pep 5 (Sahl, J. Bacteriol., 162, 833 (1985)), gallidermin (Kellner et al, Eur. J. Biochem. 177, 53 (1988)), mersacidin, actagardine (Kettenring et al., J. Antibiotics, 53, 1082 (1990)), cinnamycin (Kessler et al., Helv. Chim. Acta, 71, 1924 (1988)), duramycin, and ancovenin (Wakamiya et al., Tetrahedron Lett 26, 665 (1985)). The lantibiotic can be naturally occurring or produced by genetic engineering techniques. Compounds such as these are known and can be made in accordance with known procedures, or variations thereof that will be apparent to those skilled in the art" (pages 2-3). The disclosure goes on to teach that "[t]he structure of duramycin is known. See Hayashi et al., J. Antibiotics, 43, 1421 (1990). Duramycin is available from Sigma Chemical Co. (St. Louis, Mo., USA) as catalog no. D3168, or can be produced in accordance with known techniques from Streptovercillum cinnamoneum subsp. azacolutum (NRRL B-1699) (available from the USDA Agricultural Research Service, Peoria, Ill., USA) in accordance with known techniques. See, e.g., Hayashi et al., supra, Pridham et al, Phytopathology 46, 575-581 (1956); Shotwell et al., J. Am. Chem. Soc. 80, 3912 (1958); S. Nakamura et al. Biochem 23,385 (1984)."

The prior art teaches that lantibiotics are bacteriocins (protein toxins elaborated by bacteria to kill other bacteria) with the unique structural features of having intramolecular rings formed by thioether amino acids lanthionine (Lan) and methylanthionine (MeLan), which led to the designation lantibiotics (lanthionine-containing antibiotics) [page 64 of Guder et al, Biopoly, 2000). Guder et al. goes on to teach that "Lanbiotics do not form a homogeneous group regarding size, structure, or

mode of action.” Based on chemical and structural features, Jung suggested a subdivision of the lantibiotics into type A and B groups. Nisin, identified in 1928, belongs to type A (elongated, flexible molecules that are positively charged and act on bacterial membranes by the formation of pores). Type B lantibiotics such as ancovenin, duramycin and cinnamycin have globular structures due to their characteristic head-to-tail-cross linkage and usually carry a negative or no net charge and interfere with various enzyme functions. Additionally, compared to the cinnamycin-like type B lantibiotics, mersacidin and actagardine show a much higher degree of antimicrobial activity.

The claims are drawn, to using any lantibiotic, regardless of structure or activity, for the treatment of dry eye. The specification does provide examples of what methods are encompassed by the claimed invention (see, e.g, disclosure, pages 7-9), however, these are limited to treating dry eye disease with duramycin (Examples 1-2: drawn to duramycin application to humans and albino rabbits). It is unquestionable claim 1 is a broad generic with respect all possible methods of treatment of dry eye disease with lantibiotics encompassed by the claims. It must not be forgotten that the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is “not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.” MPEP 2163. Here, though the claims may recite a small common structural characteristic [i.e., use of lantibiotics are protein toxins created by bacteria to kill other bacteria, whose only common structural feature is having intramolecular rings formed by thioether amino acids lanthionine (Lan) and methyllanthionine (MeLan) with different activities depending on specific sequences], the claims lack written description because there is no disclosure of a correlation

between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of treatment with lantibiotics of class A, cinnamycin-type B and so forth and/or other lantibiotics with different functional activity (e.g., pages 65-70 of Guder et al.). The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomas (US 5,811,446) in view of Blackburn et al. (US 4,980,163).

Thomas teaches a method of treating blepharitis (eyelid bacterial inflammation which reads upon "dry eye disease") [e.g., column 1, line 39; column 5, lines 1-27]

comprising administering to a subject in need of such treatment a therapeutically effective amount of a broad range antibiotic to kill the bacteria that cause the blepharitis (e.g., column 3, line 24) and a saline solution carrier (e.g., column 9, line 18) via topical administration (e.g., column 9, lines 50-53; column 10, lines 30-36). Thomas also teaches antibiotic compositions acting preferably against *Staphylococcus sp.*, specially, e.g., *S. aureus* (column 5, lines 1-18). The limitation of claim 3: --wherein said administering involves topical administration—is taught, e.g., in column 10, lines 30-36. The limitation of claim 4: --wherein said topical administration is via a carrier vehicle selected from a group consisting of drops of liquid, liquid washes, gels, ointments, sprays and liposomes—e.g., column 9, lines 50-53; column 10, lines 17-29. The limitation of claim 5: --wherein said topical administration comprises infusion of said compound to said ocular surface via a device selected from a group consisting of a pump-catheter system, a continuous or selective release device and a contact lens—is taught, e.g., in column 9, lines 50-53. The limitation of claim 6: --wherein said administering is systemic administration of said compound—is taught, e.g., in column 10, lines 39-40. The limitation of claim 8: --administration of an oral form of said compound such that a therapeutically effective amount of said compound contacts lacrimal tissues of said subject via systemic absorption and circulation—is taught, e.g., column 10, lines 55-60. The limitation of claim 9: --administration of an injectable form of said compound, such that a therapeutically effective amount of said compound contacts lacrimal tissues of said subject via systemic absorption and circulation—is taught, e.g., in column 10, lines 37-40. The limitation of claim 11: --administration of an intra-

operative instillation of a gel, cream, powder foam, crystals, liposomes, spray or liquid suspension form of said compound, such that a therapeutically effective amount of said compound contacts the lacrimal tissues of said subject via systemic absorption and circulation-- is taught, e.g., column 10, lines 17-29.

Thomas does not teach using the broad range antibiotics duramycin, nisin, lysostaphin, cinnamycin, ancovenin or Pep 5.

Blackburn et al. teach broad range antibiotic compositions (e.g., abstract) comprising duramycin, lysostaphin, nisin, cinnamycin, ancovenin and Pep 5 (e.g., claims 1 and 9) which target *S. aureus* (e.g., claim 19). The limitation of claim 2: --wherein the antibiotic is duramycin-- is taught, e.g., in claim 9 of Blackburn et al. The limitation of claim 3: --wherein said administering involves topical administration—is taught, e.g., in column 3, lines 44-48. The limitation of claim 4: --wherein said topical administration is via a carrier vehicle selected from a group consisting of drops of liquid, liquid washes, gels, ointments, sprays and liposomes—is taught, e.g., in column 3, lines 44-47 and column 4, lines 10-15. The limitation of claim 6: --wherein said administering is systemic administration of said compound—is taught, e.g., in column 3, lines 44-48. The limitation of claim 8: --administration of an oral form of said compound such that a therapeutically effective amount of said compound contacts lacrimal tissues of said subject via systemic absorption and circulation—is taught, e.g., column 3, line 7. The limitation of claim 11: --administration of an intra-operative instillation of a gel, cream, powder foam, crystals, liposomes, spray or liquid suspension form of said compound, such that a therapeutically effective amount of said compound contacts the lacrimal

tissues of said subject via systemic absorption and circulation-- is taught, e.g., column 3, lines 44-48. The limitation of claim 7: --wherein said systemic administration involves administration of a nebulized liquid to oral or nasopharyngeal airways of said subject-- such that a therapeutically effective amount of said compound contacts lacrimal tissues of said subject via systemic absorption and circulation-- and the limitation of claim 10: --administration of a suppository form of said compound, such that a therapeutically effective amount of said compound contacts lacrimal tissues of said subject via systemic absorption and circulation--are not expressly taught by either reference.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Thomas by using a broad range antibiotic composition comprising duramycin, lysostaphin, nisin, cinnamycin, ancovenin or Pep 5 as taught by Blackburn et al. The skilled artisan would have been motivated to do so because Thomas teaches using a broad range antibiotic (e.g., column 3, line 24) to kill the bacteria that cause the blepharitis (column 1, line 39; column 5, lines 1-27), and the duramycin antibiotic composition taught by Blackburn is a broad range antibiotic (e.g., claims 1 and 9). There would have been a reasonable expectation of success, given that both Thomas and Blackburn teach that the antibiotic compositions are preferably effective against *Staphylococcus aureus* (e.g., column 5, lines 1-18 of Thomas, claim 19 of Blackburn et al.) that can be topically administered (e.g., column 3, lines 44-48 of Blackburn et al. and column 10, lines 30-36 of Thomas). The adjustment of particular conventional working conditions (e.g., using other forms of administration, such as nebulization or suppositories) is deemed merely a matter of judicious selection and

routine optimization that is well within the purview of the skilled artisan. As such, it would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g., suitable modes of administration), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation. One would have had a reasonable expectation for success because such modifications are routinely determined and optimized in the art through routine experimentation.

From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments

Applicants respectfully submit the Examiner has misunderstood the nature of the problem to be solved. The present claims are directed to a method of treating dry eye disease. Dry eye disease results from abnormalities of the precorneal tear film characterized by a decrease in tear production or an increase in tear film evaporation (see page 1, lines 17-19 of the specification). Therefore, one of ordinary skill in the art would recognize that the problem to be solved is not the provision of an antibiotic for treating a bacterial infection, but instead the provision of a compound that can increase or restore deficits in tear film production.

As a result of mischaracterizing the problem to be solved, Applicants respectfully submit the Examiner has also not established that there were a finite number of identifiable and predictable solutions for treating dry eye disease. Thomas does not suggest that any antibiotic, much less lantibiotics, are capable of increasing tear film production. All of the exemplified antibiotics listed in column 8, lines 7-14, are referenced solely for their antibiotic activities, not their ability to increase tear film production. Similarly, Blackburn only teaches the antibiotic properties of nisin and lysostaphin and how these properties can be enhanced when used in combination. Applicants submit that it cannot be argued that there are a finite number of identifiable and predictable solutions when neither Blackburn nor Thomas has established that lantibiotics can be used for increasing tear film production.

Further, Applicants submit that, regardless of the rationale used, the Examiner has not established a reasonable expectation of success. The Examiner concedes that Thomas teaches away from the use of beta-lactams and fluoroquinolone. However, the Examiner contends this would only motivate one of skill in the art to look at other classes of antibiotics. The Examiner alleges that Thomas suggests that broad range antibiotics in particular would be useful in treating ocular infections. Thomas teaches that histidine may be useful in treating inflammation associated with ocular diseases and trauma (Column 4, lines 27-37). Since inflammation is a common sequela of many ocular diseases (Column 4, lines 55-57), Thomas suggest that it may be useful to co-administer histidine with "a broad range of presently available ocular therapeutics" (Column 7, lines 52-55). Nowhere does Thomas specifically suggest that broad

range antibiotics would be a desirable option in treating ocular infections. Therefore, the Examiner's assertion that one of ordinary skill in the art would be motivated to try broad range antibiotics based on the teaching of Thomas is factually incorrect. In addition, the issues raised by Thomas regarding toxicity and effectiveness of antibiotics in treating ocular infections cannot be ignored. The prior art must be considered in its entirety, including disclosures that teach away from the claims. Given the toxicity and effectiveness issues raised by Thomas, it cannot be argued that one of ordinary skill in the art would have a reasonable expectation of successfully the provision of an antibiotic for treating a bacterial infection, but instead the provision of a compound that can increase or restore deficits in tear film production.

As a result of mischaracterizing the problem to be solved, Applicants respectfully submit the Examiner has also not established that there were a finite number of identifiable and predictable solutions for treating dry eye disease. Thomas does not suggest that any antibiotic, much less lantibiotics, are capable of increasing tear film production. All of the exemplified antibiotics listed in column 8, lines 7-14, are referenced solely for their antibiotic activities, not their ability to increase tear film production. Similarly, Blackburn only teaches the antibiotic properties of nisin and lysostaphin and how these properties can be enhanced when used in combination. Applicants submit that it cannot be argued that there are a finite number of identifiable and predictable solutions when neither Blackburn or Thomas has established that lantibiotics can be used for increasing tear film production.

Further, Applicants submit that, regardless of the rationale used, the Examiner has not established a reasonable expectation of success. The Examiner concedes that Thomas teaches away from the use of beta-lactams and fluoroquinolone. However, the Examiner contends this would only motivate one of skill in the art to look at other classes of antibiotics. The Examiner alleges that Thomas suggests that broad range antibiotics in particular would be useful in treating ocular infections. Thomas teaches that histidine may be useful in treating inflammation associated with ocular diseases and trauma (Column 4, lines 27-37). Since inflammation is a common sequela of many ocular diseases (Column 4, lines 55-57), Thomas suggest that it may be useful to co-administer histidine with "a broad range of presently available ocular therapeutics" (Column 7, lines 52-55). Nowhere does Thomas specifically suggest that broad range antibiotics would be a desirable option in treating ocular infections. Therefore, the Examiner's assertion that one of ordinary skill in the art would be motivated to try broad range antibiotics based on the teaching of Thomas is factually incorrect. In addition, the issues raised by Thomas regarding toxicity and effectiveness of antibiotics in treating ocular infections cannot be ignored. The prior art must be considered in its entirety, including disclosures that teach away from the claims. Given the toxicity and effectiveness issues raised by Thomas, it cannot be argued that one of ordinary skill in the art would have a reasonable expectation of successfully.

Response to Arguments

Applicants' arguments have been fully considered but they are not persuasive for the following reasons:

Contrary to Applicants' assertions, Thomas does teach treating ocular inflammations and blepharitis [inflammation of the eyelids] and keratoconjunctivitis with histidine and antibiotics which are active agents (e.g., column 3, lines 20-25; column 5, lines 27; column 7, lines 52-64; column 8, lines 5-15). Antibiotics such as broad spectrum penicillin, ciprofloxacin, ofloxacin, norfloxacin, cefazolin, tobramycin, gentamycin, amoxicillin, cephalosporin, ampicillin, carbemecillin, bacitracin and so forth are taught to be active agents in the treatment of the diseases (such as blepharitis, keratoconjunctivitis and ocular inflammations in general). Further, Applicant's statement regarding that "Thomas directs one of skill in the art away from the use of any antibiotics to treat dry eye diseases" has been considered but is not persuasive because column 3, lines 12-14 states that "Many antibiotics (e.g., beta-lactams and certain fluoroquinolones) are not well tolerated, give rise to toxicities, or are of moderate efficacy." For the reasons stated in column 3, lines 2-14, one skilled in the art would actually be motivated to look away from antibiotics such as beta-lactams and fluoroquinolones (which have undesired characteristics), and therefore the novel compositions of Blackburn with enhanced broad range bactericides (including duramycin, a lantibiotic) and activity against *S. aureus* (e.g., claims 2 and 19) would have been a desirable option in the treatment of microbial infections such as blepharitis and keratoconjunctivitis (e.g., col. 5, lines 2-40), especially because of their broad range antibiotic properties (e.g., column 7, lines 60-64; column 8, lines 1-15 of Thomas), activity against *S. aureus* (e.g., column 5, lines 15-22 of Thomas) and did not belong to the category of beta-lactams or fluoroquinolones which were known to have had toxicity,

tolerance and efficacy problems. Furthermore, Blackburn teaches that the lantibiotics are not toxic (e.g., column 3, lines 33-43).

With respect to Applicant's arguments regarding the tear production, it is noted that such limitation is not expressly stated in the instant claims. The claims, as currently drafted, are drawn to the treatment of dry eye disease. The instant disclosure does teach that " Any type of dry eye disease may be treated by the methods and compositions of the present invention, including but not limited to includes keratoconjunctivitis sicca (KCS), age-related dry eye, Stevens-Johnson syndrome, Sjogren's syndrome, ocular cicatrical pemphigoid, blepharitis, Riley-Day syndrome, and congenital alacrima. Dry eye disease can also be caused by nutritional disorders or deficiencies (including vitamins), pharmacologic side effects, eye stress and glandular and tissue destruction, environmental exposure to smog, smoke, excessively dry air, airborne particulates, autoimmune and other immunodeficient disorders, and comatose patients who are unable to blink." (disclosure, page 2, lines 15-25). Thus, reducing inflammation due to bacterial infection reads upon "treating dry eye disease" as instantly claimed.

With regards to Applicant's assertions regarding toxicity and efficacy, it is noted that nowhere in Blackburn it is indicated that duramycin, nisin and lysostaphin and so forth have any toxicity that may preclude the use of such antibiotics (See, e.g., claims). It is restated that the teaching away in Thomas is from beta-lactams and fluoroquinolones, which are not of the same category as the instantly claimed

lantibiotics. More importantly, Blackburn teaches that the lantibiotics are not toxic (e.g., column 3, lines 33-43).

Hence, there is reasonable expectation of success in using the lantibiotics of Blackburn in the method of treating dry eye (blepharitis, keratoconjunctivitis) of Thomas because the lantibiotics of Blackburn are broad spectrum antibacterials effective against *S. Aureus*, which were effective as active agents as shown by Thomas (e.g., column 7, lines 60-64; column 8, lines 1-15 of Thomas), and because they were known to be non-toxic and safe for topical application [e.g., column 3, lines 33-65 of Blackburn and column 10, lines 30-36 of Thomas].

With regards to the unexpected results arguments, it is noted that the evidence presented is not commensurate with the scope of the claims and that the argued limitation of tear film regeneration is not expressly stated in the instant claims as drafted.

Therefore, the obviousness rejection is maintained.

Double Patenting

The ODP rejection of record over US 7,479,481 is withdrawn in view of the Terminal Disclaimer filed 2 March 2009 which has been approved.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCELA M. CORDERO GARCIA whose telephone number is (571)272-2939. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Anish Gupta/
Primary Examiner, Art Unit 1654

/Marcela M Cordero Garcia/
Patent Examiner, Art Unit 1654

MMCG 05/09